Strategies to improve monitoring disease progression, assessing cardiovascular risk, and defining prognostic biomarkers in chronic kidney disease

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Chronic kidney disease (CKD) is a major global public health problem with significant gaps in research, care, and policy. In order to mitigate the risks and adverse effects of CKD, the International Society of Nephrology has created a cohesive set of activities to improve the global outcomes of people living with CKD. Improving monitoring of renal disease progression can be done by screening and monitoring albuminuria and estimated glomerular filtration rate in primary care. Consensus on how many times and how often albuminuria and estimated glomerular filtration rate are measured should be defined. Meaningful changes in both renal biomarkers should be determined in order to

ascertain what is clinically relevant. Increasing social awareness of CKD and partnering with the technological community may be ways to engage patients. Furthermore, improving the prediction of cardiovascular events in patients with CKD can be achieved by including the renal risk markers albuminuria and estimated glomerular filtration rate in cardiovascular risk algorithms and by encouraging uptake of assessing cardiovascular risk by general practitioners and nephrologists. Finally, examining ways to further validate and implement novel biomarkers for CKD will help mitigate the global problem of CKD. The more frequent use of renal biopsy will facilitate further knowledge into the underlying etiologies of CKD and help put new biomarkers into biological context. Real-world assessments of these biomarkers in existing cohorts is important, as well as obtaining regulatory approval to use these biomarkers in clinical practice. Collaborations among

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academia, physician and patient groups, industry, payer organizations, and regulatory authorities will help improve the global outcomes of people living with CKD.

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Chronic kidney disease (CKD) is a major global public health problem, and the economic, health care, and social impact of CKD is substantial.¹ Recent healthy life expectancy and disability-adjusted life-years (DALYs) data show that although health is improving globally, DALYs due to CKD have increased by 19.6% between 2005 and 2015.² The prevalence and associated burden of CKD and kidney failure is rising worldwide, with the fastest growth occurring in low-income countries (LIC) and low middle-income countries (LMIC).^{2–4} In order to mitigate the risks and adverse effects of CKD, the global nephrology community under the leadership of the International Society of Nephrology (ISN) created a cohesive set of activities called “Closing the Gaps” (www.theisn.org) to improve the global outcomes of people living with CKD. One of these activities included a meeting held in Vancouver, Canada in July 2016, which put forth the following initiatives: to identify and prioritize key activities for the next 5 to 10 years in the domains of clinical care, research, education, and advocacy; to identify potential partners within and outside the nephrology community; and to create an action plan and performance framework. This paper expands on the recently published ISN CKD Roadmap⁵ and focuses on strategies to improve the monitoring of renal disease progression, improve the prediction of cardiovascular (CV) events in CKD, and examine ways to further validate and implement novel biomarkers for disease progression (Table 1).

Improving the monitoring of renal disease progression

The estimated glomerular filtration rate (eGFR) and albuminuria are the current guideline-recommended biomarkers to monitor renal disease progression in CKD. These biomarkers are strong predictors of adverse renal outcomes, as well as cardiovascular disease (CVD) and mortality.^{6,7} Additionally, these biomarkers have been shown to be strong predictors of renal and CV outcomes in various patient settings, including the general population. While the nephrology and diabetes guidelines recommend measuring albuminuria and eGFR over time in patients with CKD, it is unclear how often albuminuria and eGFR should be measured in general practice. Day-to-day variability in albuminuria has been thought to affect its predictive power; however, recent studies have shown that this may not be the case. Multiple urine sampling does not improve the prediction of CV-related death when using the urine albumin-creatinine ratio as a

continuous variable, except at very low ranges.⁸ Another recent study showed that a single first morning void sample for risk prediction equals the average of the first morning void samples obtained on 3 consecutive days.⁹ A consensus needs to be met regarding how often albuminuria and eGFR should be measured to predict risk and/or enrich clinical trials for patients at risk for CKD and CVD.

Albuminuria is measured over time to monitor the disease progression and response to treatment. Although nephrology guidelines recommend albuminuria monitoring over time, the implementation of guidelines for regular monitoring of albuminuria and eGFR in the primary care setting in both LIC-LMIC and high-income countries is lacking and represents a major challenge. ISN’s aim is that within 5 years, 20% of the countries that do not currently measure albuminuria and eGFR in a primary care setting will have implemented these markers to monitor the prognosis of patients at risk of CKD and CVD, such as the elderly and patients with diabetes mellitus and/or hypertension. Collaboration with physicians, policy makers, and guideline developers is necessary to implement such screening programs. Furthermore, long-term monitoring is important because risk can change over time. One study showed that incorporating multiple albuminuria measurements over time in risk algorithms may be more appropriate to monitor treatment effects and quantify renal risk.¹⁰

An important unanswered question, which will help the clinical implementation of albuminuria monitoring, relates to the identification of what changes in albuminuria and eGFR over time are clinically meaningful and how these changes are associated with clinical outcomes and actions. Recent studies illustrated that changes in albuminuria over time are strongly and consistently associated with the risk of end-stage kidney disease and death.¹¹ Furthermore, compared with normoalbuminuria, sustained microalbuminuria, remitted microalbuminuria, and the development of macroalbuminuria are associated with a higher risk of CV events and reduced eGFR.¹² Moreover, it is important to determine whether higher levels of GFR (e.g., eGFR > 60 ml/min per 1.73 m²) without albuminuria should be included in CKD definition, given that CKD prevalence, sex ratios, and Kidney Disease: Improving Global Outcomes composite risk groupings vary widely depending on the eGFR equation used.¹³ The scientific community should therefore address if G1 and G2 (i.e., GFR > 60 ml/min per 1.73 m²) without albuminuria should be included in the CKD definition or if these stages merely reflect the “normal aging” process. Although these studies provide important data on the use of albuminuria and eGFR, they were single studies, and the kidney community would benefit from a large meta-analysis of multiple cohort studies to precisely delineate what changes in albuminuria and/or eGFR are associated with clinically meaningful risks. Therefore, a large collaborative effort is needed to combine multiple observational cohort studies to address this question, such as the Chronic Kidney Disease Prognosis Consortium. Collaboration with other professional organizations, such as the

Table 1 | Improving the monitoring of renal disease progression and prediction of cardiovascular disease and facilitating the identification, validation, and implementation of novel prognostic biomarkers in chronic kidney disease⁵

Goals	Activities	Partners	Possible Deliverables
Improve monitoring of kidney disease progression in patients with CKD	Implement regular measurements of albuminuria and eGFR	Policy makers, professional societies, patient advocacy groups, guideline developers, WHO	Increase in the number of countries capable of measuring albuminuria and eGFR
	Increase awareness and empower patients in self-management and understanding of their health (e.g., by implementing health technology applications)	Patient organizations, print and electronic media, ISN	Formal interactions with partners to develop collaborations to accomplish goals (e.g., International Federation of Kidney Foundation)
	Define changes in albuminuria and eGFR that are meaningful for individual patients and how they relate to clinical action	Scientists, FDA, EMA	Report on optimal change in albuminuria and association with outcome International collaboration with ongoing initiatives (e.g., NKF/FDA/EMA workshop)
Improve CVD risk prediction in patients with CKD	Develop a risk prediction tool that integrates albuminuria and eGFR in the CVD risk assessment of patients with CKD	Nephrologists, endocrinologists, cardiologists, general practitioners, if possible renal pharmacists	Web-based risk scores for CVD involving renal risk markers (albuminuria/eGFR) Evidence of use of risk scores in clinical practice
Facilitate identification, validation, and implementation of prognostic biomarkers in CKD	Sustain and enhance efforts to identify and validate biomarkers that indicate the progression and/or therapeutic responsiveness of CKD	Regulatory authorities (e.g., FDA, EMA), industry partners, payers	Conferences with partners to develop guidelines and principles
	Sustain and enhance efforts to identify and validate biomarkers that indicate the development of CVD events in patients with CKD	EUTox, CKD biomarkers consortium, industry partners	Conferences with partners Correlation of uremic toxins to disease phenotype Increased acceptance and use of diagnostic tests for specific conditions

CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; EUTox, European Uremic Toxin Work Group; FDA, Food and Drug Administration; ISN, International Society of Nephrology; NKF, National Kidney Foundation; WHO, World Health Organization.

National Kidney Foundation and American Society of Nephrology, or regulatory agencies, such as the Food and Drug Administration and European Medicines Agency, would also be beneficial. Once these studies are completed, their conclusions should be rapidly incorporated into international practice guidelines and their results disseminated to end-users.

Increasing social awareness of CKD is another important activity to improve the monitoring of CKD. Furthermore, we need to empower patients with CKD for self-management and their understanding of the disease. There is a need for coordinated and individualized supportive care in order to optimize the quality of care for patients with CKD in both LIC-LMIC and high-income countries. The global nephrology community needs to not only involve and collaborate with patient organizations, such as the International Federation of Kidney Foundation, but also facilitate patients to be more active in their own care (e.g., shared decision making). Patient-centered care is a means of achieving better health outcomes and greater patient satisfaction through shared decision making.¹⁴ Communication avenues, such as social and electronic media, should be utilized to improve awareness of CKD. Furthermore, better education of medical care providers is

needed to support patients with CKD. Nephrologists have reported feeling inadequately prepared to deal with end-of-life challenges inherent in the care of their patients.¹⁵ Tools for physicians are needed for them to better engage in patient-centered decision making.¹⁶ To accomplish these goals, we suggest that a formal interaction with patient stakeholder groups is developed within the next 2 years. Since the screening for prediabetes and diabetes has been shown to be feasible in the dental office¹⁷ and by pharmacists,¹⁸ these health care facilities should be given the opportunity to screen for albuminuria in the general population.

Technological advances in societal and medical fields present an opportunity to engage patients and medical care providers in the monitoring of CKD. In this regard, the kidney community should seek collaborations with the technology industry to take advantage of the ongoing evolution of information technology and implement new health technology applications worldwide. However, for the development of these apps, factors such as ease of use, language, layout, and costs, need to be taken into account, especially for the use of these apps by the elderly.¹⁹ Patients and physicians alike should be involved in the app development process.²⁰

Improving the prediction of CVD in patients with CKD

Compared with the general population, CVD is more frequent and severe in patients with CKD. Moreover, it is often not recognized and thus undertreated. Patients with CKD should be viewed among the highest-risk groups for CVD, and they require special clinical attention at an individual patient level.²¹ Current CV risk algorithms are based on traditional CV risk factors and do not include the renal markers albuminuria or eGFR, which have been shown to improve upon traditional CV risk factors.⁶ Implementation of these renal risk markers to monitor renal disease and CVD progression could represent a major step forward in the management of CVD in CKD. Since measuring albuminuria and eGFR is relatively inexpensive, it would be feasible to implement these renal risk markers in LIC-LMIC. Furthermore, the screening of renal disease should be included in a comprehensive clinical history for the prevention of CVD.²² Noteworthy, CKD is mainly associated with 2 types of CVD: accelerated atherosclerosis and specific CKD-related CVD, including arteriosclerosis and cardiac abnormalities.²³ Improving the care of patients with CKD through efficient and personalized CVD risk assessment related to these 2 types of CVD will be a significant challenge.

In order to improve CVD risk prediction in CKD, the renal community needs to develop risk prediction tools applicable to patients with CKD in collaboration with other medical specialty groups (e.g., endocrinologists, cardiologists, gerontologists, and general practitioners) and the pharmaceutical industry. An important activity within this goal is to sustain and enhance efforts to identify the development and risk of CV events in the CKD population and vice versa. Although renal risk markers are strong predictors of CV events,²¹ they are currently not included in CV risk algorithms. A novel CV risk score for hemodialysis patients was recently introduced (<http://aro-score.askimed.com>).²⁴ We believe that ISN could play an instrumental role in facilitating the assessment of the need for novel, web-based CV risk algorithms that include renal risk markers albuminuria and eGFR. Additionally, ISN should foster collaborations with partners that are already working actively in the area of CV complications in patients with CKD.

The heterogeneous and often unknown etiology of CKD, though most often caused by diabetes, hypertension, vascular disease, and glomerulonephritis, may result in different populations of CKD patients around the globe. However, the etiology of CKD remains uncertain in a large proportion of affected individuals, hindering the prevention and cause-specific treatment. It should therefore be investigated whether different risk prediction models should be used in various populations and ethnicities and whether these risk prediction models are equally predictive in high-income countries versus LIC-LMIC.²⁵

Another problem that needs consideration is the lack of evidence that existing CV risk prediction models are being used regularly in clinical nephrology or internal medicine settings. This may be because the clinical usefulness of these models is not established (i.e., whether the use of these models improves

clinical outcomes of patients). Supporting initiatives to identify barriers in the implementation of CV risk models in clinical practice and determining how they can be overcome should be prioritized. Additionally, the training of young researchers on all aspects of prognostic model research, from discovery to clinical implementation, is another issue that could be picked up by the kidney community.

Identification, validation, and implementation of novel prognostic biomarkers

ISN has defined a goal of developing and testing new therapeutic strategies in order to improve the global problem of CKD. One strategy to achieve this goal is to facilitate the identification, validation, and implementation of novel biomarkers in CKD. As mentioned previously, eGFR and albuminuria are the classical guideline-endorsed biomarkers to monitor renal disease progression in CKD. These biomarkers are strong predictors of renal disease progression, as well as CVD and mortality. However, the clinical triggers of albuminuria and eGFR (the presence of sustained micro-albuminuria or eGFR < 60 ml/min per 1.73 m²), when physicians begin to initiate treatment (e.g., lifestyle or pharmacological intervention), already indicate a (possibly irreversibly) diseased kidney. Reduced eGFR is the consequence of compromised kidney function and substantial loss and destruction of the glomeruli, and the presence of micro-albuminuria indicates a permeable glomerular basement membrane and/or tubular injury. Importantly, renal damage in early disease stages rarely shows clinical characteristics, so on the everyday clinical level, early-stage diagnosis and tailored treatment for CKD are not adequate (i.e., the preventive treatment is not initiated early enough). In order to improve patient outcomes and reduce associated health care costs, timely detection and prevention of CKD progression are needed.

The past decade has published a large number of papers on novel biomarkers in CKD (Table 2). Unfortunately, most of the identified novel biomarkers did not move past the discovery phase of development. With the exception of cystatin C-calculated eGFR, the only clinically accepted biomarkers for monitoring renal disease are albuminuria and serum creatinine-calculated eGFR. However, before a biomarker can be used in clinical practice, it needs to be extensively validated in order to assess its effect on patient management and outcomes. Unfortunately, many biomarker studies in CKD are limited by small sample sizes, heterogeneous results, and a lack of large validation studies. As a result, most novel biomarkers do not progress further down the biomarker pipeline into validation and clinical utility stages. Thorough external validation of new biomarkers and assessment of clinical utility is usually lacking. This is likely because the implementation of new biomarkers into practice is a process full of pitfalls and limitations. Clear guidance as to how to develop and validate new biomarkers is limited, though lessons on biomarker qualification may be learned from other research communities.²⁶ Furthermore, increased awareness and investment is

Table 2 | Novel biomarkers in chronic kidney disease

Study	Biomarker	Study design	Sample size	Study population	Length of follow-up
Bhavsar et al. <i>Am J Kidney Dis.</i> 2011;58:886–893. ³⁴	Plasma BTP and cystatin C	RCT/observational cohort	865	Hypertensive African Americans and CKD	8.5 yr
Desai et al. <i>Am J Kidney Dis.</i> 2011;58:717–728. ³⁵	Serum Tnt and NT-pro-BNP	Nested RCT	995	Type 2 diabetes with baseline eGFR of 20–60 ml/min per 1.73 m ²	3.5 yr
Isakova et al. <i>JAMA.</i> 2011; 305:2432–2439. ³⁶	Plasma FGF-23	Prospective	3879	CKD stage 2–4	3.5 yr
Niewczas et al. <i>J Am Soc Nephrol.</i> 2012;23: 507–515. ³⁷	Plasma TNFR1 and TNFR2	Prospective	410	Type 2 diabetes	8–12 yr
Wong et al. <i>Kidney Int.</i> 2013; 83:278–284. ³⁸	Plasma TGF- β 1 and BMP-7	Nested RCT	281	Type 2 diabetes	5 yr
Sabbisetti et al. <i>J Am Soc Nephrol.</i> 2014;25: 2177–2186. ³⁹	Plasma KIM-1	Prospective	124	Type 1 diabetes and proteinuria	5–15 yr
Fufaa et al. <i>Diabetologia.</i> 2015;58:188–198. ⁴⁰	Urinary L-FABP and NGAL	Prospective	260	Pima Indians with type 2 diabetes	14 yr
Hayek et al. <i>N Engl J Med.</i> 2015;373:1916–1925. ⁴¹	Plasma suPAR	Prospective	3683	Adults with cardiovascular disease	6 yr

BMP-7, bone morphogenetic protein 7; BTP, beta-trace protein; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; KIM-1, kidney injury molecule-1; L-FABP, liver type fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; RCT, randomized controlled trial; suPAR, soluble urokinase-type plasminogen activator receptor; TGF- β 1, transforming growth factor beta 1; TNFR1, tumor necrosis factor receptor 1; TNFR2, tumor necrosis factor receptor 2; Tnt, troponin.

needed to perform well-powered studies that appropriately address the clinical utility and clinical outcome phases in order to implement the use of novel biomarkers in clinical practice.

Novel biomarkers may improve the identification of CKD, namely during its early stages, and identify renal disease aspects that are not well monitored by eGFR or albuminuria (i.e., tubular damage, renal inflammation, and fibrosis). Novel biomarkers could also play different roles in diagnosis, prognosis, and monitoring by improving the risk stratification, helping increase our understanding of renal disease pathophysiology and providing insight into novel therapeutic targets. Novel biomarkers could improve our understanding of the underlying molecular mechanisms of renal disease progression. Thus, it should be determined how novel biomarkers change during disease progression or with therapy and how these changes predict clinical outcomes or improve our understanding of CKD progression. A number of novel opportunities to improve risk prediction are currently emerging. The development of high-throughput screening techniques (e.g., omics, such as transcriptomics, proteomics, and metabolomics) provides the opportunity to better understand the natural course of CKD.²⁷ For example, the past decade of proteomics and metabolomics studies in diabetic nephropathy have increased our knowledge of molecular mechanisms involved in its pathogenesis.^{28,29} Unfortunately, at the moment, there is no alternative assay technology that can replace mass spectrometric approaches for these biomarkers. Furthermore, due to higher costs and infrastructure requirements, such novel biomarkers may not be easily utilized in LIC-LMIC.

The availability of renal biopsy tissue can facilitate the development of biomarkers of renal progression. Renal

histopathology is considered the gold standard by which novel biomarker levels are compared in animal studies. Therefore, the examination of patient biopsies is the only viable route for the qualification of renal diagnostic biomarkers in humans. Interestingly, the addition of gene expression measurements to transplant biopsy specimens in renal transplantation may facilitate the stratification of patients at high risk for graft loss.³⁰ The current international Kidney Disease: Improving Global Outcomes guideline recommends a renal biopsy to establish a specific renal diagnosis in addition to the staging of CKD based on eGFR and albuminuria. Although this is not feasible in the vast majority of CKD cases, the ability to identify underlying etiologies contributing to albuminuria and GFR decline would significantly aid in the development of prognostic models and novel biomarkers by reducing heterogeneity and misclassification. Observational studies have estimated that up to 20% of the cases with CKD would have another secondary or alternative diagnosis if biopsies were performed. A retrospective study of renal biopsy findings in diabetic patients showed that nondiabetic renal disease is coexistent with diabetic nephropathy in approximately one-third of such biopsies. On biopsy, 37% of patients had diabetic nephropathy alone, 36% had nondiabetic renal disease alone, and 27% had diabetic nephropathy plus nondiabetic renal disease.³¹ In several situations, especially in nonproteinuric and early-stage CKD, existing clinical models do not perform well and albuminuria measurements are not useful. In these scenarios, a biopsy would ideally be the main prognostic tool to guide disease progression. However, we realize that there are significant barriers to this ideal practice of obtaining biopsies that need to be addressed. The expansion of obtaining biopsies in patients with CKD will require education and training, capacity building at local institutions

and regional centers, and registries development to compare biopsy findings across centers and settings.

Real-world assessments of the performance of biomarkers should be performed to determine whether or not they make a difference to patient care and thus should be integrated (or not) into clinical practice.³² To this end, the renal community should take advantage of existing large, observational cohort studies with bio-banked samples and long-term follow-ups to perform studies needed to determine effective risk thresholds and cost-effectiveness. ISN believes that rapid advancements in database management that allow for the sharing of databases can help create large databases to validate novel biomarkers. This requires the development of standardized definitions, methods of data collection and storage, and some minimal standard dataset across countries. Individual investigators need to be willing to share data while of course guaranteeing patient privacy.

In order to sustain and enhance efforts to identify and validate biomarkers for monitoring the progression and/or therapeutic responsiveness of CKD, the global renal community needs to partner with all CKD stakeholders. Collaborations between academia, industry, existing consortia, and regulatory authorities are needed to share expertise from different areas and promote the effective dissemination of results. Patient and advocacy groups and payer organizations are important stakeholders in biomarker development in CKD and are key partners who can strongly advocate for greater investment in kidney disease trials. Physicians need to be onboard with novel technologies and developments in CKD research as they are the ones who need to adopt best practices and utilize tools to ensure the standardization of care. Collaboration with regulatory authorities is important to align relevant drug development pathways. For example, in collaboration with the European Uremic Toxin Work Group,³³ industry, and regulatory agencies, ISN could arrange a stakeholder meeting within the next year to reach a consensus on which biomarkers or uremic toxins promote a prematurely aged vascular uremic phenotype and define a strategy on how these markers should be targeted.

Conclusion

CKD is a global problem with significant gaps in research, care, and policy. Despite its considerable health care burden, CKD is ranked among the most neglected noncommunicable diseases. ISN has recognized these gaps and developed a comprehensive plan for systematic progress. Ways to improve the monitoring of renal disease progression have been put forward. The screening and monitoring of albuminuria and eGFR in primary care need to be done. Consensus on how many times and how often albuminuria and eGFR are measured should be defined. Furthermore, meaningful changes in both renal biomarkers should be determined in order to ascertain what is clinically meaningful. Increasing the social awareness of CKD and partnering with the technological community may be ways to engage patients. Another important area is to improve the prediction of CV events in

patients with CKD. This could be achieved by including the renal risk markers albuminuria and eGFR in CV risk algorithms. Encouraging the assessment of CV risk by general practitioners and nephrologists may be a step toward better CV risk prediction. Finally, examining ways to further validate and implement novel biomarkers for CKD will help mitigate the global problem of CKD. Not only identifying new biomarkers but also moving these biomarkers forward to validation and clinical utility needs to be a research priority. The more frequent use of renal biopsies will further expand our knowledge into the underlying etiologies of CKD and help put new biomarkers into biological context. Real-world assessments of these biomarkers in existing cohorts and collaborations among academia, physician and patient groups, industry, payer organizations, and regulatory authorities are important for biomarker qualification. Working to achieve these strategies will help improve the global outcomes of people living with CKD.

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